

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
PATENT EXAMINING OPERATION

Applicant(s): DODDA MOHAN RAO et al.

Serial No: 10/524,478

Group Art Unit: 1626

Filed: 02-11-2005

Examiner: LOEWE, SUN JAE Y

Att. Docket No.: S2096/20001

Confirmation No.: 6950

For: NOVEL CRYSTALLINE FORM OF LINEZOLID

**SECOND DECLARATION OF D. MOHAN RAO, PH.D. UNDER 37 C.F.R. § 1.132**

Mail Stop RCE  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I, D. Mohan Rao, a citizen of India, hereby declare and state:

1. I am a co-inventor of the subject matter described and claimed in the present application.

2. I am the Managing Director of Symed Laboratories Limited, with more than 25 years of experience in the Pharmaceuticals Industry. The resume attached as **Appendix 1- A** to the First Declaration of D. Mohan Rao accurately reflects my professional credentials.

3. I understand from my attorneys that 37 C.F.R. 41.203(a) sets forth:

(a) Interfering subject matter. An interference exists if the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party and vice versa.

4. I understand from my attorneys that for a prior art reference to anticipate the claims, the reference must teach every element of the claims.

5. I understand from my attorneys that finding obviousness requires that the prior art reference (or references when combined) must teach or suggest all the claim limitations and that

there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

6. While I am not an expert in patent law, my experience and educational background enable me to render an informed opinion as to the facts underlying the determination of obviousness, including: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness, such as commercial success, long-felt but unsolved need, failure of others, copying, and unexpected results.

7. The present application claims a crystalline linezolid form III, characterized by an x-ray powder diffraction spectrum having peaks expressed as  $2\theta$  at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees, and further characterized by an IR spectrum having main bands at about 3338, 1741, 1662, 1544, 1517, 1471, 1452, 1425, 1400, 1381, 1334, 1273, 1255, 1228, 1213, 1197, 1176, 1116, 1082, 1051, 937, 923, 904, 869, 825 and 756  $\text{cm}^{-1}$ , wherein there is at least a 99.8% enantiomeric excess of the linezolid form III.

8. I have carefully reviewed U.S. Patent Application No. 11/171,098 (Aronhime et al.).

9. For the reasons discussed below, I believe that the facts support a conclusion that the subject matter of the claims of the instant application would, if prior art to the '098 application, have anticipated or rendered obvious the subject matter of the claims of the '098 application, and vice versa.

10. Using the methods described in the '478 application, I and/or researchers under my direct supervision prepared linezolid polymorphic form III, and evaluated the linezolid polymorphic

form III using X-ray powder diffraction (XRPD) analyses. The XRPD analyses were carried out utilizing a Bruker AXS D8 ADVANCE X-ray powder diffractometer. A  $2\theta$  theta continuous scan (1 sec/0.030° step) from 2.00 to 50.000°  $2\theta$  was used.

11. The obtained XRPD data for the linezolid polymorphic form III is set forth in **Appendix 2 - A**.

12. The linezolid polymorphic form III XRPD comprised peaks at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 deg  $2\theta$ .

13. The Teva '098 application discloses that the linezolid polymorphic form (identified as "form IV") XRPD comprised peaks at about 7.5, 13.5, 18.0, 18.7, 19.9, 21.1, 22.2, 25.4, 27.7, and 28.4 deg  $2\theta$  (see '098 application at Figure 1, attached as **Appendix 2 - B**).

14. It is my opinion that the subject matter of the claims of the instant application would, if prior art, have anticipated and/or rendered obvious the subject matter of the instant claims of the Teva '098 application, and vice versa, based on a comparison of the XRPD data, since the XRPD data show that the powder diffraction patterns comprise identical peaks. The peaks at 19.9 deg  $2\theta$  and 28.4 deg  $2\theta$  which are present in Teva's XRPD pattern are also present in Symed's XRPD pattern (see **Appendix 2 - A** and **Appendix 2 - B**).

15. Using the methods described in the instant application, I and/or researchers under my direct supervision prepared linezolid polymorphic form III, and evaluated the linezolid polymorphic form III using Fourier-transform infrared (FT-IR) spectroscopy. The FT-IR of linezolid polymorphic form III was obtained on a FT-IR 8300 Shimadzu instrument, in the range of 400-4000  $\text{cm}^{-1}$  with a resolution of 2[1/cm].

16. The obtained FT-IR spectra of the linezolid polymorphic form III is set forth in

**Appendix 2 - C.**

17. The linezolid polymorphic form III FT-IR spectrum comprised peaks at 2817, 1335, 1229, 1200, and 662  $\text{cm}^{-1}$ .

18. The Teva '098 application discloses that the claimed linezolid polymorphic form (identified as "form IV") FT-IR spectrum comprised peaks at 2817, 1335, 1229, 1200, and 662  $\text{cm}^{-1}$  (see '098 application at Figure 2d, attached as **Appendix 2 - D**). The '098 application further sets forth that linezolid polymorphic form (identified as "form IV") has an FTIR spectrum with peaks at about 3333, 2817, 1732, 1661, 1540, 1515, 1335, 1256, 1229, 1200, 1213, 1148, 1080, 1059, 1050, 903, 825, 755, and 662  $\text{cm}^{-1}$ .

19. It is my opinion that the subject matter of the claims of the instant application would, if prior art, have anticipated and/or rendered obvious the subject matter of the claims of the '098 application, and vice versa, based on a comparison of the FT-IR data.

20. As set forth in the First Declaration of D. Mohan Rao, Ph.D., using the methods described in the application, I and/or researchers under my direct supervision prepared linezolid polymorphic form III, and evaluated the linezolid polymorphic form III using differential scanning calorimetry (DSC). The DSC thermographs were obtained using a TA Instruments DSC Q200 instrument at a scan rate of 10.00°C/min over a temperature range of 40-220°C.

21. The DSC thermogram of linezolid polymorphic form III is attached as **Appendix 1 - B** to the First Declaration of D. Mohan Rao, Ph.D.

22. The linezolid polymorphic form III DSC thermogram had an endothermic peak at 178.96°C.

23. The Teva '098 application discloses that the claimed linezolid polymorphic form

(identified as "form IV") DSC thermogram had an endothermic peak at 179.07°C (see '098 application at Figure 3, attached as **Appendix 2 - E**).

24. It is my opinion that the subject matter of the claims of the instant application would, if prior art, have anticipated or rendered obvious the subject matter of the claims of the '098 application, and vice versa, based on a comparison of the DSC thermograms.

25. In addition, I and/or researchers under my direct supervision prepared linezolid polymorphic form II, and evaluated the linezolid polymorphic form II using differential scanning calorimetry (DSC).

26. The DSC thermogram of linezolid polymorphic form II is attached as **Appendix 1 - C** to the First Declaration of D. Mohan Rao, Ph.D.

27. The linezolid polymorphic form II DSC thermogram has endothermic peaks at 155.32 °C and 179.06°C, and an exothermic peak at about 159°C.

28. The Teva '098 application discloses that linezolid polymorphic form II has a DSC thermogram with endothermic peaks at around 155°C and 180°C, and an exothermic peak at around 160°C (see '098 application at Figure 8, attached as **Appendix 2 - F**).

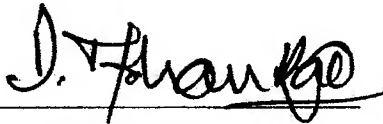
29. It is my opinion that the linezolid polymorphic form II as in the claims of the '098 application is the same linezolid form II polymorph as used in the instant application based on a comparison of the DSC thermograms.

30. Accordingly, I believe that the facts support a conclusion that the subject matter of the claims of the instant application would, if prior art, have anticipated or rendered obvious the subject matter of the claims of the '098 application, and vice versa, and thus the claims of the instant application and the '098 application are directed to interfering subject matter.

Application No. 10/524,478  
Declaration Under 37 C.F.R. § 1.132

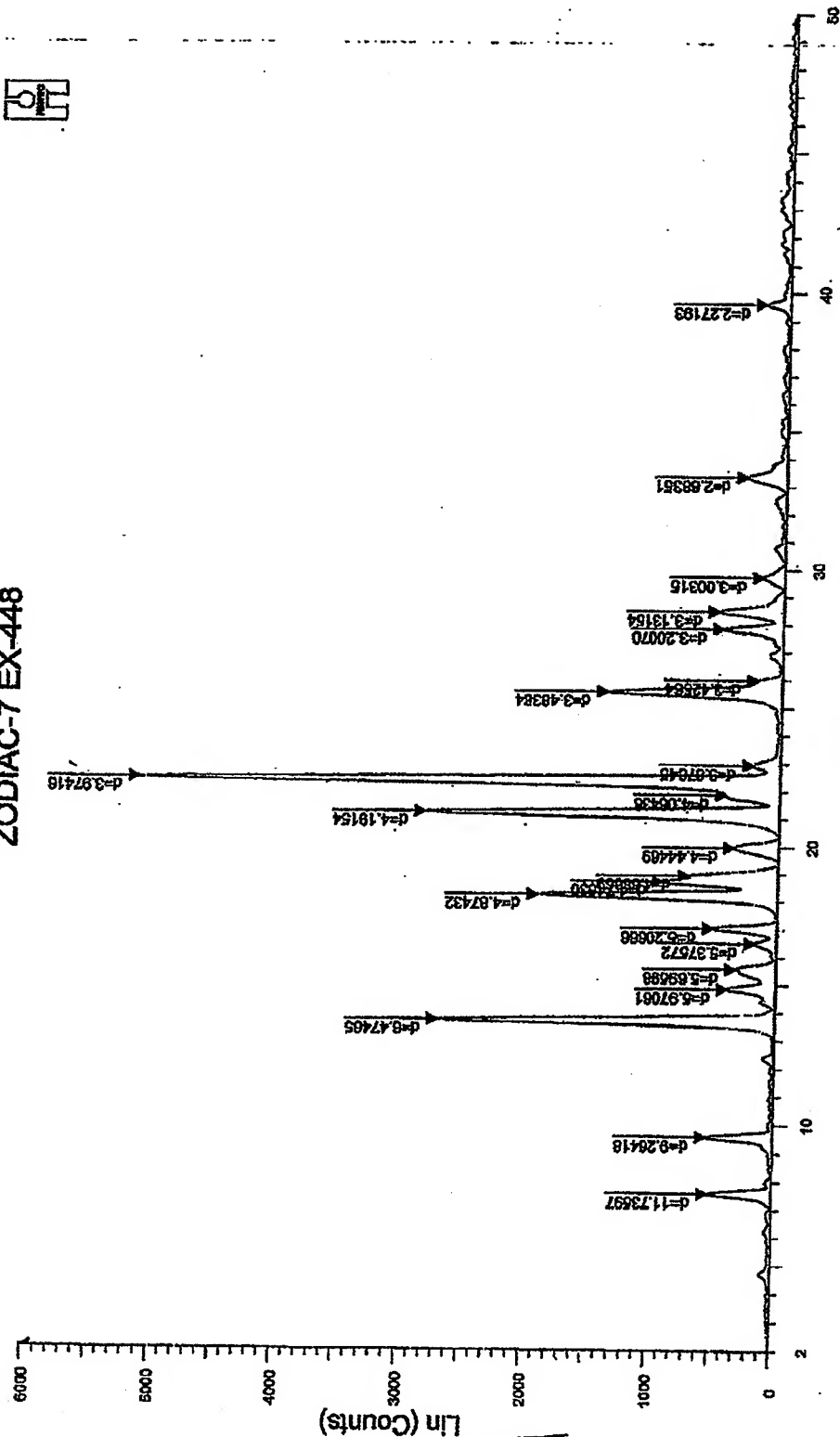
31. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: 3/06/2009

  
D. Mohan Rao, Ph.D.

## **Appendix 2 - A**

# ZODIAC-7 EX-448



File: ZODIAC-7 EX-448.raw - Type: 2Th/Th locked - Start: 2.000 ° - End: 50.000 ° - Step: 0.020 ° - Step time: 1. s - 2-Theta: 2.000 ° - Creation: 03-Apr-04 15:44:05  
 Operations: Smooth 0.150 | Background 0.977,1.000 | Import

Tested by: See

3 April 2004

Checked by: Minif

3 April 2004



**Product Name** : ZODIAC-7 EX-448

**File Name** : C:\DIFFDAT\ZODIAC-7 EX-448 raw

SNo.	Angle 2-Theta °	d value Angstrom	Intensity % %
1	7.527	11.73597	9.80
2	9.539	9.26418	10.20
3	13.666	6.47466	52.30
4	14.825	5.97061	7.20
5	15.544	5.69598	6.00
6	16.477	5.37572	3.10
7	17.016	5.20666	9.60
8	18.185	4.87432	37.10
9	18.684	4.74530	17.50
10	18.920	4.68669	13.80
11	19.960	4.44469	6.50
12	21.179	4.19154	54.90
13	21.850	4.06438	8.10
14	22.352	3.97416	100.00
15	22.923	3.87645	3.90
16	25.548	3.48384	26.90
17	25.958	3.42968	3.90
18	27.852	3.20070	9.00
19	28.480	3.13154	9.80
20	29.726	3.00315	3.00
21	33.363	2.68351	5.70
22	39.638	2.27193	3.40

Tested by: SRB  
03-04-04 16:45

Checked by: [Signature]  
03-04-04 16:45

## **Appendix 2 - B**

X-Ray powder diffractogram of Linezolid Form IV.

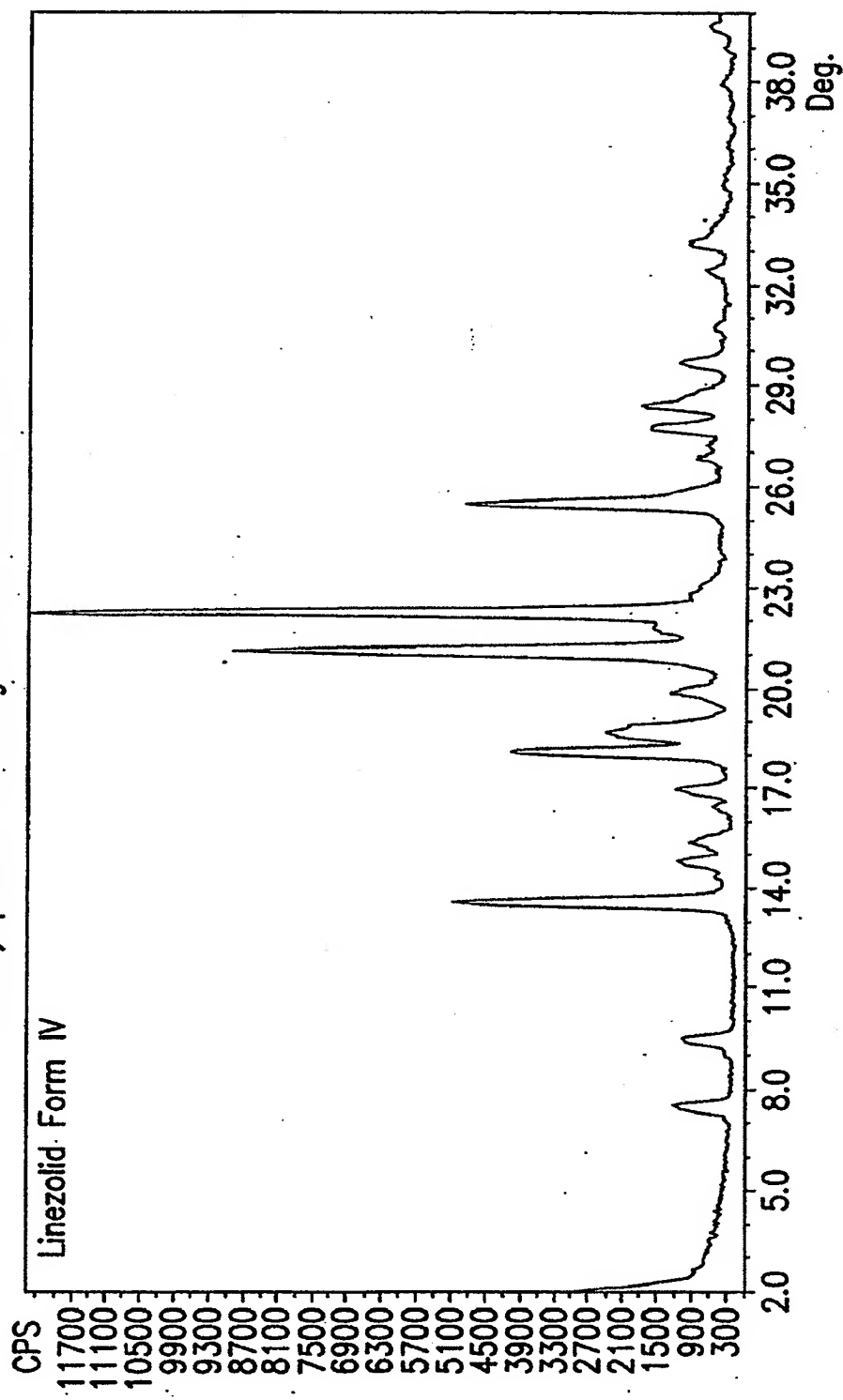
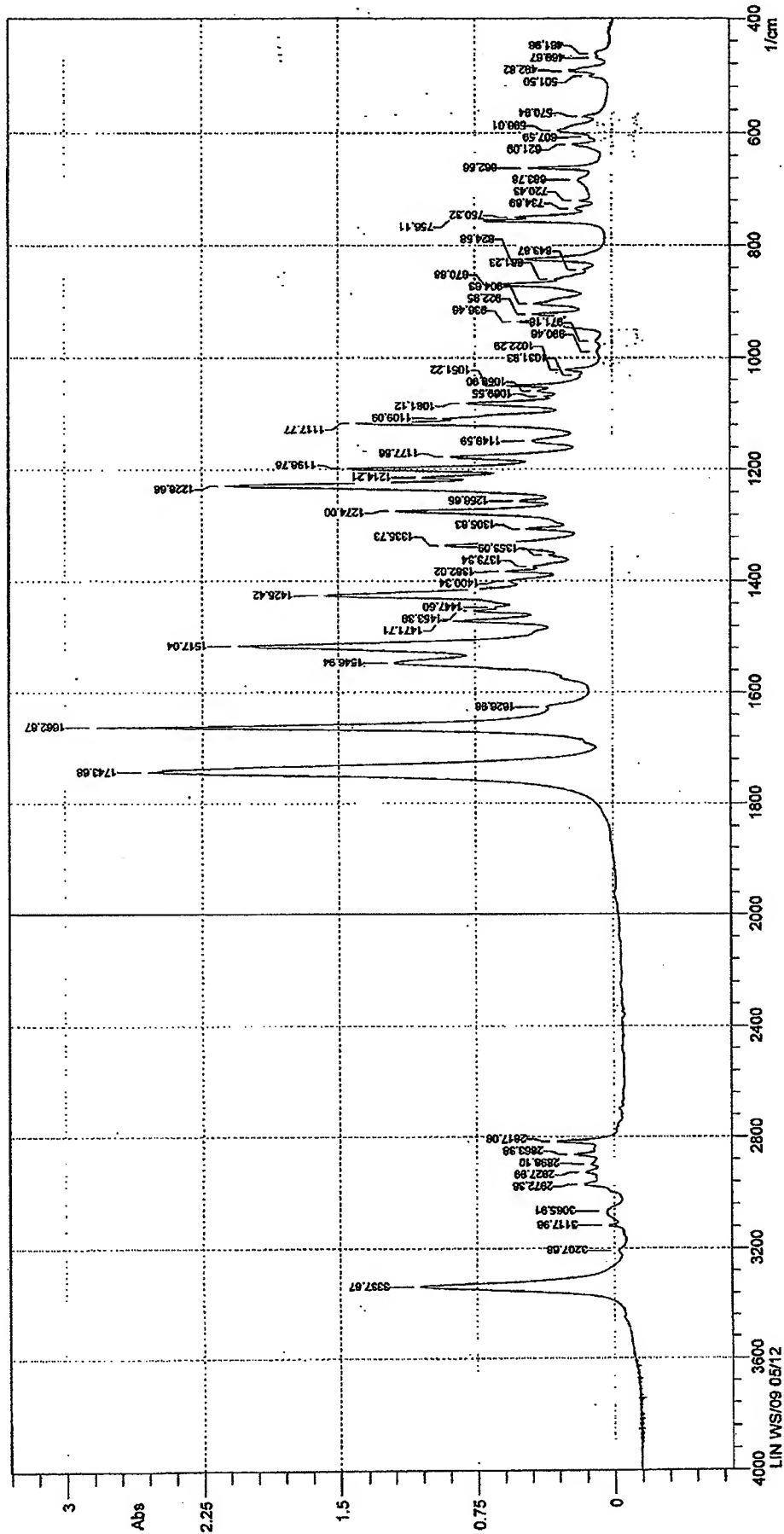


FIG. 1

## **Appendix 2 - C**

# SYMED LABS LIMITED



Resolution; 2 [1/cm]  
 No. of Scans; 20  
 Apodization; Happ-Genzel

Comment;  
 LIN WS/09 05/12

Date/Time; 5/21/2009 10:36:16 AM

D:\DATA-2009\MAY-2009\LIN WS2105091.smf

User; IRUSER *Ch. gub*  
 21.05.09

## **Appendix 2 - D**

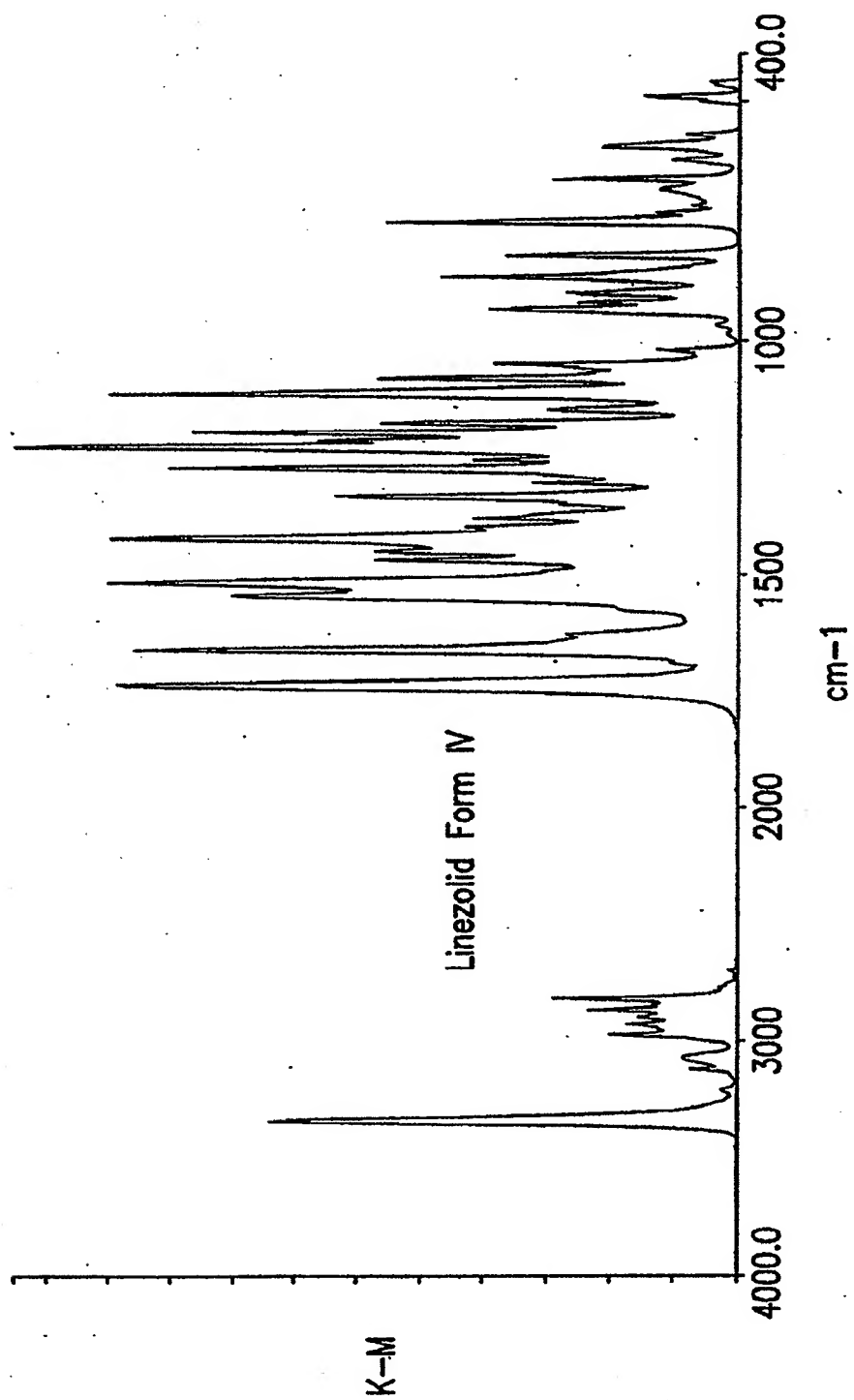


FIG. 2d

## **Appendix 2 - E**



# DSC thermogram of Linezolid Form IV.

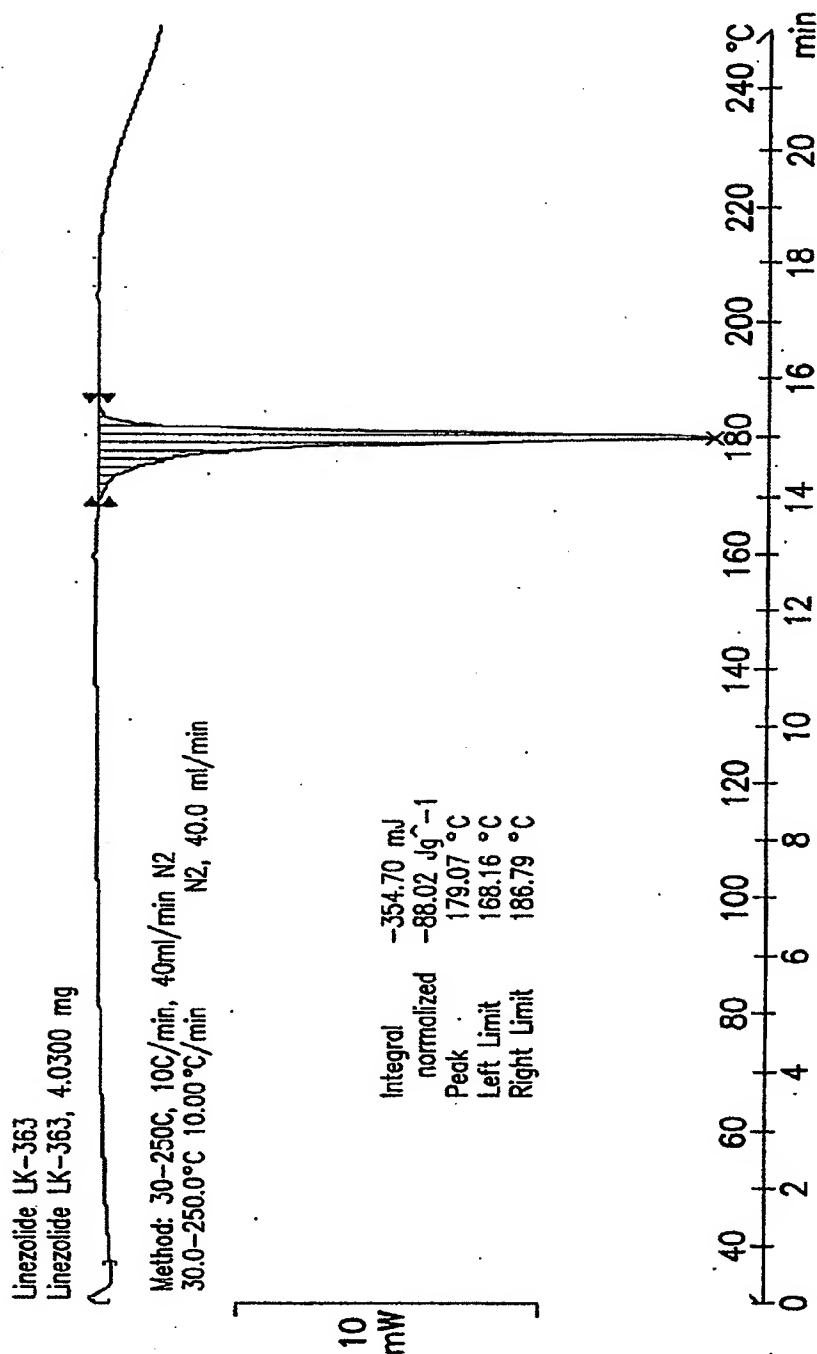


FIG.3

## **Appendix 2 - F**

# DSC thermogram of Linezolid Form II.

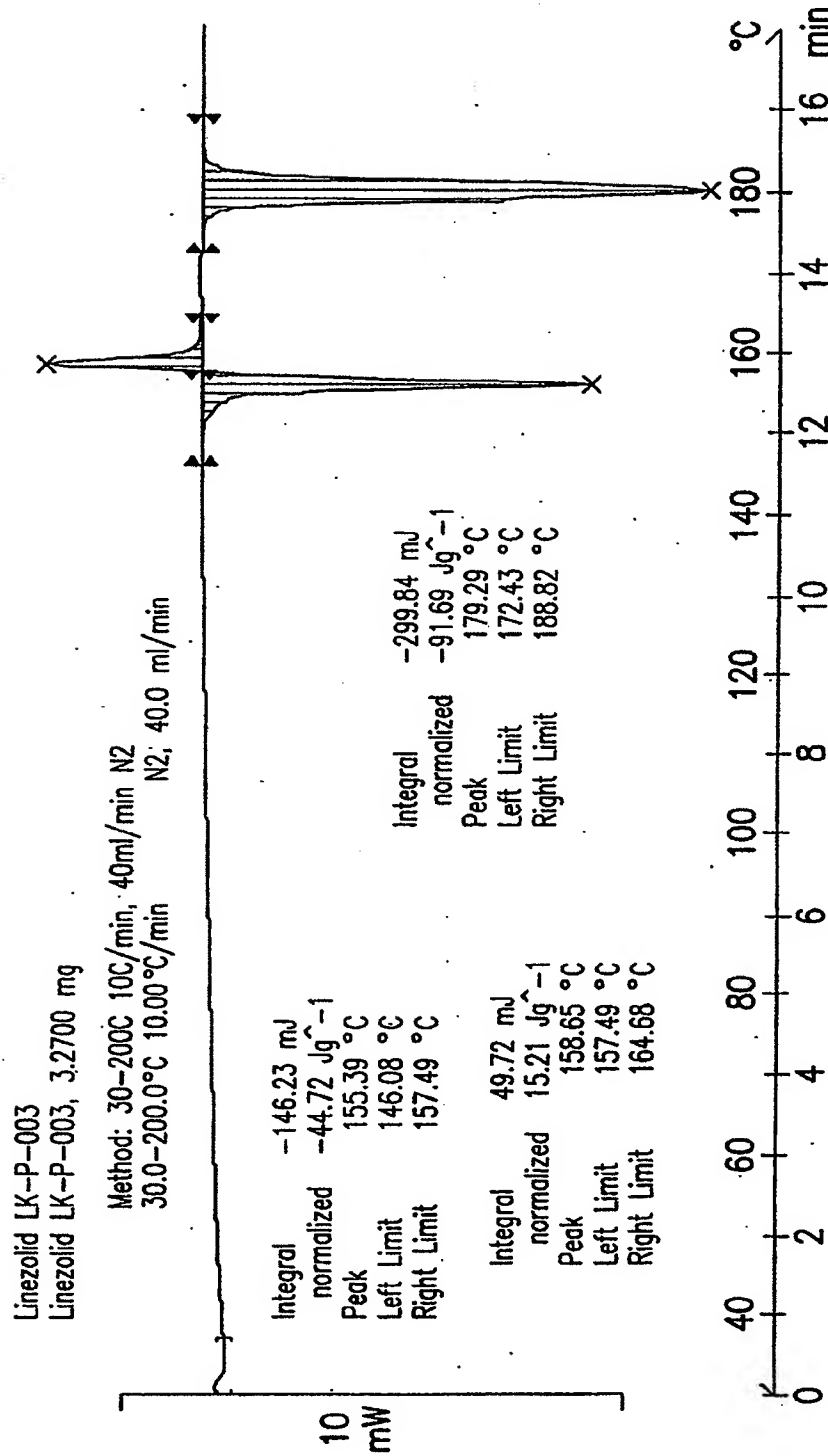


FIG.8